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Relation between tumor FDG uptake and hematologic prognostic indicators in stage I lung cancer patients following curative resection

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Abstract

Hematologic parameters of systemic inflammation are receiving attention as promising prognostic indicators in cancer patients. Here, we investigated the relation and compared the prognostic values of circulating blood cell-based parameters and tumor ^{18}F-fluoro-2-deoxyglucose (FDG) uptake in patients with stage I nonsmall cell lung cancers (NSCLC).

Subjects were 1034 patients with newly diagnosed stage I NSCLC who underwent FDG positron emission tomography/computed tomography (PET/CT) followed by curative resection. Total white blood cell (WBC) count, absolute neutrophil, lymphocyte and platelet counts, neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) were obtained. Tumor FDG uptake was measured as SUVmax.

WBC, neutrophil and lymphocyte counts, and NLR demonstrated weak but significant correlation to tumor SUVmax. Using the upper quartile as cutoff, patients with high tumor SUVmax had significantly higher WBC, neutrophil and lymphocyte counts, and greater NLR. There were 144 recurrences (13.9%) over a median follow-up of 29.5 months. On Cox proportional hazards regression analysis, WBC count, tumor SUVmax, age, gender, smoking, cell type, and tumor stage were significant univariate prognostic factors. On multivariate analysis, high tumor SUVmax (HR = 2.22; 95% CI, 1.52–3.25; $P < 0.001$), tumor stage 1B (HR = 2.11; 95% CI, 1.47–3.01; $P < 0.001$), and old age (HR = 1.03; 95% CI, 1.01–1.05; $P = 0.002$) were significant independent predictors of poor survival. Finally, high tumor SUVmax remained a significant predictor of prognosis in both low and WBC count groups.

Circulating blood counts showed significant correlation to tumor FDG uptake in early stage NSCLC. WBC count was a significant univariate variable, but tumor FDG uptake was a superior and independent predictor of outcome. Hence, tumor FDG uptake effectively stratified prognosis in patients with low as well as high WBC count.

Abbreviations: DFS = disease-free survival, FDG = ^{18}F-fluoro-2-deoxyglucose, HR = hazard ratio, NLR = neutrophil-to-lymphocyte count ratio, NSCLC = nonsmall cell lung cancers, PET/CT = positron emission tomography/computed tomography, PLR = platelet-to-lymphocyte ratio, SUVmax = maximum standardized uptake value, WBC = white blood cell.

Keywords: FDG, lung cancer, neutrophil-to-lymphocyte ratio, PET/CT, prognosis

1. Introduction

Lung cancer is the leading cause of cancer deaths in both men and women.[1] The most important prognostic factor for nonsmall cell lung cancers (NSCLC) that constitute approximately 85% of all lung cancers is tumor stage.[2] Patients with advanced stage NSCLC have the poorest prognosis, and only those with early-stage disease are candidates for complete resection. However, even following curative surgery, patients have a 5-year survival rate between 60% and 80%,[3] with recurrence as the major cause of mortality. As such, prognostic indicators that help predict risk of cancer relapse should allow more appropriate monitoring of patients with early-stage NSCLC following curative resection.

[18]F-fluoro-2-deoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) provides quantitative information on the metabolic activity of tumors, and is useful not only for staging and assessing treatment response but also for predicting patient prognosis. In NSCLC, metabolic parameters derived from FDG PET have been shown to provide prognostic information incremental to that obtained by conventional imaging.[4,5]

A more recent class of prognostic markers in cancer disease that is receiving intense attention is hematologic parameters of systemic inflammation based on circulating blood cell counts.[6] It is now recognized that cancer-associated inflammation plays an important role in the development and progression of most types of cancers. Furthermore, significant systemic inflammatory responses can exert negative influence on the nutritional, functional, and immunologic status of the host.[6] While the precise mechanism is currently under investigation, it is becoming

increasingly apparent that the presence and severity of systemic inflammatory responses is closely associated with the outcome of cancer patients, and therefore has significant prognostic value. Cellular components of the host hematologic system that have been linked to cancer patient survival include circulating cells of inflammation, immunity, and hemostasis. Neutrophils and lymphocytes are known to play fundamental roles in cell-mediated destruction of cancer cells.[7] Mounting recent evidence supports that blood count of these cells can help predict patient outcome in many types of cancers. Furthermore, neutrophil-to-lymphocyte count ratio (NLR), an early marker of global inflammation, has been shown to possess significant prognostic value in various tumors including NSCLC.[8,9] A similar prognostic role has also been suggested for platelet-to-lymphocyte count ratio (PLR).[8,9]

Since tumor FDG uptake is significantly influenced by intratumoral inflammatory processes,[10] it is tempting to speculate a relationship between this and hematologic predictors of cancer prognosis, but this possibility has not been previously explored. Conversely, the prognostic information provided by these parameters may be sufficiently independent, and therefore add incremental value to each other. Given the routine testing of blood cell counts in virtually all patients, it would be of significant clinical relevance to determine the prognostic association between hematologic parameters and tumor FDG uptake in patients with cancer. We thus explored the relation between tumor FDG uptake and circulating blood cell-based parameters in patients with stage I NSCLC, and further investigated their prognostic associations following curative resection. The study was performed in patients with stage I disease since the presence of metastatic lesions may confound the relation between circulating blood cell counts and tumor FDG uptake.

2. Materials and methods

2.1. Study subjects

We retrospectively reviewed consecutive patients with newly diagnosed stage 1 NSCLC, who underwent FDG PET/CT for initial staging at our institute from January 2008 to December 2012. Inclusion criteria were performance of curative surgical resection and the presence of negative resection margins, which resulted in 1035 cases. Exclusion criteria were as follows: neoadjuvant or adjuvant therapy, clinical signs of or microbiologically proven preoperative infection, recent steroid therapy, and presence of coexisting hematologic or autoimmune disorders. Thirty-nine patients presenting infectious symptom with leukocytosis (total white blood cell count ≥10,000/μL) were also excluded. Thus, a total of 1034 subjects were finally included for analysis. The study protocol was approved by our Institutional Review Board, and the need to obtain written informed consents was waived.

Clinical profiles and survival information were obtained by reviewing medical records. Tumor histology and pathologic tumor size were determined from surgical pathology reports. Histology was classified according to the WHO guidelines, and tumor staging followed the TNM classification.

2.2. ^{18}F-FDG PET/CT and uptake measurement

Patients fasted for at least 6 hours before PET/CT studies, and blood glucose level was <200 mg/dL at the time of FDG injection in all cases. At 60 minutes after injection of FDG (5.5 MBq/kg),

PET and unenhanced CT images were acquired on a Discovery STe PET/CT scanner (GE Healthcare, Chicago, IL). CT images were acquired on a 16-slice helical CT with 30 to 170 mAs adjusted to the patient's body weight at 140 kVp and 3.75 mm section width. This was followed by an emission PET scan from the thigh to the head for 2.5 minutes per bed position in 3-dimensional mode. Attenuation-corrected PET images (3.9 × 3.9 × 3.3 mm) using CT data were reconstructed with an ordered subsets expectation maximization algorithm (20 subsets, 2 iterations).

To measure the magnitude of tumor FDG uptake, regions of interest were drawn along the margin of the primary tumor on a tomographic PET/CT slice with the highest tumor activity. Uptake levels were expressed as maximum standardized uptake value (SUVmax) normalized to patient body-weight.

2.3. Parameters from blood cell count and patient grouping

Hematologic parameters were obtained from peripheral venous blood samples taken within 30 days of the PET/CT prior to surgery. Blood cell counts were measured on a fully automated counting system and confirmed by laboratory technicians. Hematologic parameters of interest included total white blood cell (WBC) count, absolute neutrophil count, lymphocyte count, and platelet count. NLR and PLR were calculated by respective cell counts.

Cut-off values were selected by receiver operating characteristics analysis. After comparing mean values and several different percentile values, upper quartile values were selected as cutoff to categorize subjects into groups with high and low hematologic parameters and FDG uptake.

2.4. Statistical analysis

Linear regression analysis was used to determine the correlation between hematologic parameters and tumor SUVmax. Disease-free survival (DFS), defined as the interval between surgery and first cancer recurrence, was determined as primary clinical outcome. The prognostic significances of variables for DFS were assessed by univariate and multivariate analyses using Cox proportional hazards regression models. Survival curves were estimated using the Kaplan–Meier method, and differences between groups were carried out with log-rank tests. SPSS 20.0 (SPSS Inc, Chicago, IL) software and MedCalc version 13.1 (MedCalc Software, Mariakerke, Belgium) were used for statistical analyses. All tests were 2-sided, and P values <0.05 were considered statistically significant.

3. Results

3.1. Clinical characteristics of the entire cohort and groups according to tumor SUVmax

The clinical characteristics of our study subjects are summarized in Table 1. The entire study cohort had a mean age of 61.6 years (range, 16–89 years); there were 609 males (58.9%); 98.5% had Eastern Cooperative Oncology Group performance status 0, and 49.4% were current or former smokers. Histological subtype was adenocarcinomas in 793 (76.7%), squamous cell carcinomas in 180 (17.4%), and unspecified types in 61 patients (5.9%). The pathologic stage was IA in 727 and IB in 307 patients. The mean tumor SUVmax was 5.5 ± 4.9.

Table 1

Demographic and clinical characteristics of study subjects.

Characteristics	Total subjects (n = 1034)	High SUVmax (n = 258)	Low SUVmax (n = 776)	P value
Age, mean ± SD, y	61.6 ± 10.0	64.7 ± 9.1	60.6 ± 10.1	<0.001
Gender				<0.001
Male	609 (58.9%)	200 (77.5%)	409 (52.7%)	
Female	425 (41.1%)	58 (22.5%)	367 (47.3%)	
ECOG performance grade 0	1019 (98.5%)	253 (98.1%)	766 (98.7%)	0.450
Never-smokers	523 (50.6%)	77 (29.8%)	446 (57.5%)	<0.001
Histology				<0.001
Squamous cell carcinoma	180 (17.4%)	115 (44.6%)	65 (8.4%)	
Adenocarcinoma	793 (76.7%)	125 (48.4%)	668 (86.1%)	
Others	61 (5.9%)	18 (7.0%)	43 (5.5%)	
Tumor stage				<0.001
Stage IA	727 (70.3%)	118 (45.7%)	609 (78.5%)	
Stage IB	307 (29.7%)	140 (54.3%)	167 (21.5%)	
Type of surgery				<0.001
Wedge resection	71 (6.9%)	7 (2.7%)	64 (8.2%)	
Segmentectomy	38 (3.7%)	6 (2.3%)	32 (4.1%)	
Lobectomy	901 (87.1%)	231 (89.5%)	670 (86.3%)	
Bilobectomy	18 (1.7%)	10 (3.9%)	8 (1.0%)	
Pneumonectomy	6 (0.6%)	4 (1.6%)	2 (0.3%)	
SUVmax, mean ± SD	5.5 ± 4.9	12.6 ± 4.1	3.1 ± 2.0	<0.001
WBC ($\times 10^3$/μL), mean ± SD	6.4 ± 1.8	6.9 ± 1.8	6.3 ± 1.8	<0.001
Neutrophil ($\times 10^3$/μL), mean ± SD	3.6 ± 1.4	3.9 ± 1.4	3.5 ± 1.4	<0.001
Lymphocyte ($\times 10^3$/μL), mean ± SD	2.1 ± 0.6	2.2 ± 0.7	2.1 ± 0.6	0.021
NLR, mean ± SD	1.8 ± 0.9	1.9 ± 1.0	1.8 ± 0.9	0.016
PLR, mean ± SD	115.4 ± 51.8	113.9 ± 45.3	115.9 ± 53.7	0.585
Disease-free survival, mo	32.9 ± 17.7	29.5 ± 18.5	34.0 ± 17.3	<0.001

NLR = neutrophil-to-lymphocyte ratio, PLR = platelet-to-lymphocyte ratio, SD = standard deviation, SUVmax = maximum standardized uptake value, WBC = white blood cell.

When a 75 percentile cut-off value of 7.83 was applied, 258 patients had high tumor SUVmax and 776 had low tumor SUVmax. Patients with high tumor SUVmax were slightly older and had greater proportions of males, ever-smokers, squamous carcinomas, and stage IB tumors (Table 1).

3.2. Blood cell counts and relation to tumor SUVmax

The results of blood cell counts are summarized in Table 1. Compared with the low SUVmax group, the high SUVmax group had significantly greater WBC, neutrophil and lymphocyte counts, and higher NLR. This prompted us to examine the relation between tumor SUVmax and blood cell parameters. As a result, linear regression analysis demonstrated weak but significant correlations of tumor SUVmax with total WBC count, neutrophil count, lymphocyte count, and NLR (Fig. 1).

3.3. Patient outcome and univariate predictors of prognosis

The study subjects were followed up for a median duration of 29.5 months. While there were no deaths during this period, locoregional or distant recurrence was documented in a total of 144 patients (13.9%). This led to an overall disease-free survival of 95% at 1 year and 90% at 2 years. DFS was significantly shorter for the high tumor SUVmax group (29.5 ± 18.5 months) compared with the low SUVmax group (34.0 ± 17.3 months; Table 1).

We next analyzed prognostic factors using univariate Cox-regression hazard models. The 75 percentile cut-off values for hematologic parameters were 7.48×10^3/μL for WBC count,

4.38×10^3/μL for neutrophil counts, 2.53×10^3/μL for lymphocyte count, 2.14 for NLR, and 135 for PLR. By definition, there were 258 patients with high value and 776 patients with low value for all parameters. Univariate analysis demonstrated that greater age, male gender, ever-smokers, squamous cancer cell type, tumor stage IB, high tumor SUVmax, and high total WBC count were significant predictors of poor prognosis. High tumor SUVmax had the greatest hazard ratio (HR) of 3.10 (95% CI, 2.24–4.31, $P < 0.001$), followed by tumor stage IB (HR = 2.94; 95% CI, 2.12–4.08; $P = 0.001$). Notably, neither NLR nor PLR was significantly associated with patient survival (Table 2).

3.4. Multivariate predictors of prognosis and survival analysis

Multivariate Cox analysis using significant univariate variables revealed that older age (HR = 1.03; 95% CI, 1.01–1.05; $P = 0.002$), tumor stage 1B (HR = 2.11; 95% CI, 1.47–3.01; $P < 0.001$), and high tumor SUVmax (HR = 2.22; 95% CI, 1.52–3.25; $P < 0.001$) were significant independent predictors for poor prognosis (Table 3). Kaplan–Meier survival analysis showing significant survival benefits of low tumor SUVmax and low total WBC count are illustrated in Fig. 2.

Finally, we performed Kaplan–Meier survival analysis in patients categorized according to tumor SUVmax and WBC count. As a result, total WBC count failed to significantly influence survival in both high and low tumor SUVmax groups (Fig. 3). In contrast, high SUVmax was significantly associated with worse survival in both high (HR, 3.33; 95% CI, 2.24–4.94; $P < 0.001$) and low WBC count groups (HR, 2.38; 95% CI, 1.31–4.33; $P = 0.004$; Fig. 3).
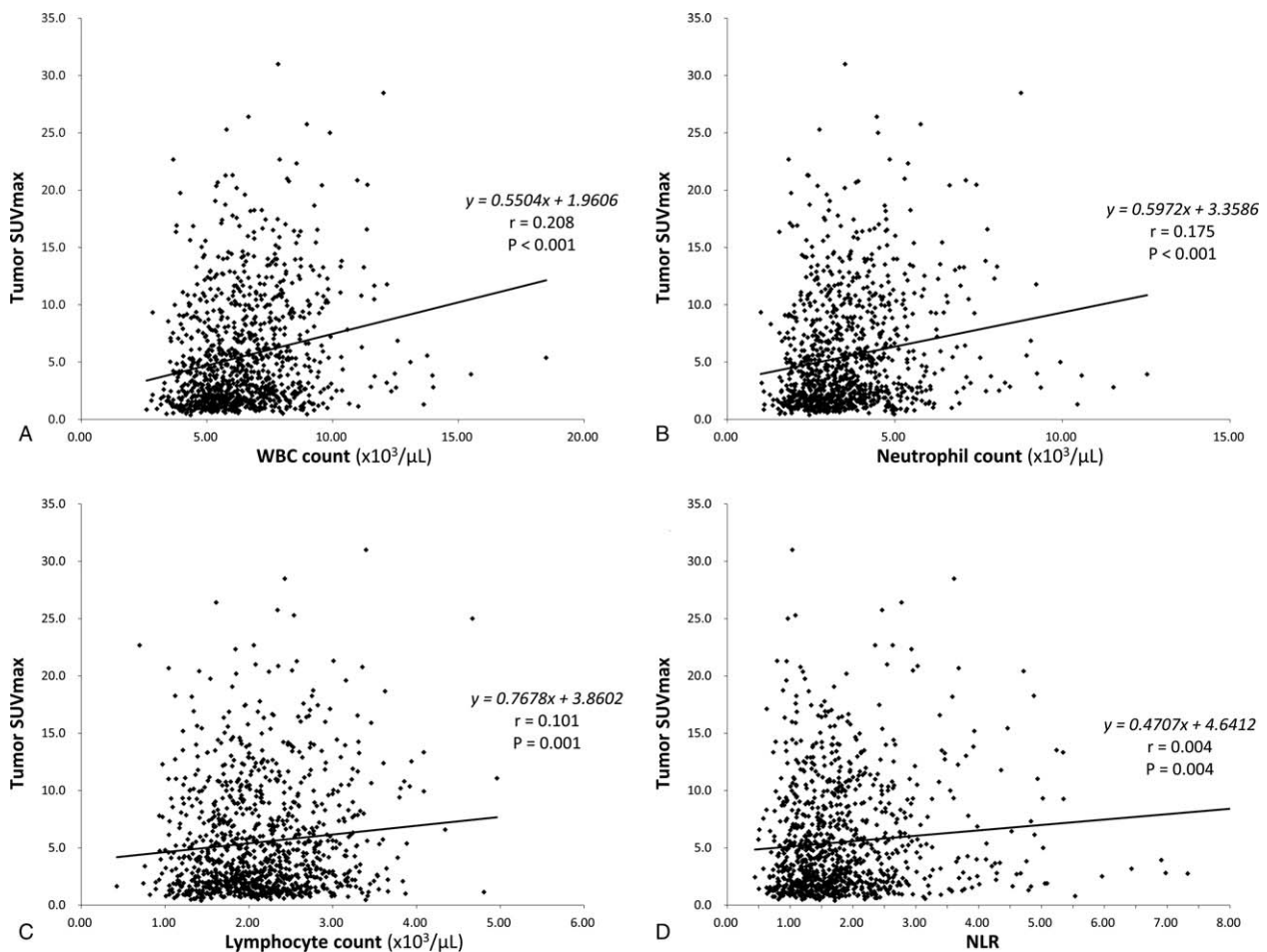
Figure 1. Correlations between tumor SUVmax and total WBC count (A), neutrophil count (B), lymphocyte count (C), and neutrophil-to-lymphocyte ratio (NLR; D). SUVmax = maximum standardized uptake value, WBC = white blood cell.

4. Discussion

In this cohort of stage I NSCLC patients, circulating white blood cell, neutrophil and lymphocyte counts, as well as NLR were found to have significant correlations with tumor FDG uptake. Accordingly, patients with high tumor SUVmax had significantly greater counts of total white blood cells, neutrophils and lymphocytes, and higher NLR compared with those with low tumor SUVmax.

Although correlations have previously been reported between blood neutrophil count and FDG uptake in the bone marrow,[11]

Table 2
Univariate Cox regression analysis of survival.

| Variables | Categories | Disease-free survival | | |
		HR	95% CI	P
Age	1 y increase	1.046	1.027–1.065	<0.001
Gender	Male vs female	1.715	1.197–2.457	0.003
Smoking	Ever-smoker vs never-smoker	1.715	1.226–2.401	0.002
Histology	Squamous vs nonsquamous	1.910	1.326–2.750	0.001
Tumor stage	Stage IB vs IA	2.939	2.118–4.080	<0.001
Surgery	P+B+L vs S+W	2.014	0.942–4.307	0.071
SUVmax	>7.83 vs ≤7.83	3.104	2.238–4.306	<0.001
WBC (×10³/μL)	>7.48 vs ≤7.48	1.487	1.043–2.121	0.028
Neutrophil (×10³/μL)	>4.28 vs ≤4.28	1.274	0.882–1.840	0.197
Lymphocyte (×10³/μL)	>2.53 vs ≤2.53	1.028	0.708–1.495	0.883
NLR	>2.14 vs ≤2.14	0.985	0.671–1.448	0.940
PLR	>135 vs ≤135	1.129	0.782–1.631	0.517

B = bilobectomy, CI = confidence interval, HR = hazard ratio, L = lobectomy, NLR = neutrophil-to-lymphocyte ratio, P = pneumonectomy, PLR = platelet-to-lymphocyte ratio, S = segmentectomy, SUVmax = maximum standardized uptake value, W = wedge resection, WBC = white blood cell.

Table 3

Multivariate Cox regression analysis of survival.

Variables	Categories	DFS		
		HR	95% CI	P
Age	(1 y increase)	1.031	1.011–1.051	0.002
Gender	Male vs female	1.181	0.685–2.037	0.550
Smoking	Ever-smoker vs never-smoker	1.188	0.709–1.990	0.513
Histology	Squamous vs nonsquamous	1.425	0.913–2.224	0.119
Tumor stage	Stage IB vs IA	2.105	1.473–3.007	<0.001
SUVmax	>7.83 vs ≤7.83	2.222	1.518–3.254	<0.001
WBC ($\times 10^3$/μL)	>7.48 vs ≤7.48	1.070	0.737–1.554	0.723

CI = confidence interval, DFS = disease-free survival, HR = hazard ratio, SUVmax = maximum standardized uptake value, WBC = white blood cell.

to our knowledge, this is the first demonstration that circulating blood cell counts can correlate to tumor FDG uptake. While the basis underlying this weak but significant association is not clear, a possible link may be found in intratumoral inflammatory processes that can contribute to tumor FDG activity.[10] Infiltrating macrophages, granulocytes, and lymphocytes have been shown to elevate tumor FDG accumulation, especially when the cells are activated.[12] Conversely, many tumors can secrete inflammatory cytokines that promote systemic inflammation processes. Indeed, one of the causes of elevated WBC count in cancer patients is production of granulocyte colony stimulating factor (G-CSF) by the tumor, and some NSCLCs can secrete G-CSF into the blood in quantities sufficient to raise peripheral WBC counts.[13] Furthermore, patients with G-CSF-producing tumors are reported to show abnormally high tumor FDG uptake with histopathologic findings of increased inflammatory cell infiltration.[14] However, these possibilities were not pursued in the present study, and further studies will be required to clarify this issue. Another possible explanation for our observed correlation is that high tumor FDG uptake and elevated inflammatory cell counts are indirectly associated through their link with tumor aggressiveness.

When Cox regression analysis of DFS was performed, total WBC count and tumor SUVmax, in addition to several clinical factors, were identified as significant univariate predictors of outcome. A WBC count threshold based on the 75 percentile value was able to stratify favorable from poor prognosis. Although the hazards ratio by this variable was relatively small, the clinical implication is potentially large because hematologic parameters are widely available from simple, inexpensive, and reproducible blood tests. Notably, however, neither neutrophil count nor NLR was able to show significant prognostic value in our study cohort. Moreover, total WBC count, which was the only significant univariate variable among hematologic parameters, did not show significant independent prognostic value when adjustment for other univariate variables was performed by multivariate analysis. This finding is divergent from the findings of several recent studies that report significant prognostic associations of 1 or more hematologic parameters in patients with NSCLC. Tomita et al[15] previously found total WBC and platelet counts to be significant univariate and multivariate predictors of outcome in 289 patients with NSCLC. In a more recent study, this group found NLR to be a significant univariate and multivariate indicator of prognosis in 84 patients with stage IV NSCLC.[16] Similar prognostic values for NLR were also observed by Kacan et al[17] in 299 NSCLC patients, Sarraf et al[18] in 177 NSCLC patients, and Pinato et al[8] in 220 NSCLC patients who underwent surgical resection, and Cedres et al[19] in 171 NSCLC patients with stage IV disease. Furthermore, positive associations were not restricted to advanced stage disease. Zhang et al[20] studied 400 NSCLC patients with pN0 disease and observed total WBC count, lymphocyte count, neutrophil count, NLR, and PLR as univariate predictors, and NLR as a multivariate predictor of survival following curative resection. In the report of Sarraf et al,[18] NLR was able to stratify prognosis in 83 of the study subjects who had stage I disease. Cannon et al[21] evaluated 149 patients with early-stage NSCLC and found NLR to be a significant univariate and multivariate predictor of prognosis.

Although the majority of previous studies in patients with lung cancer report positive associations with outcome, hematologic parameters have not always been shown to provide significant
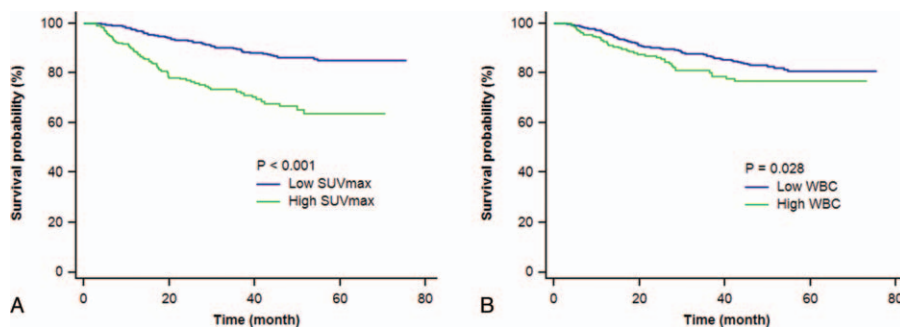

Figure 2. Kaplan–Meier curves of disease-free survival of study subjects (n = 1034) stratified by tumor SUVmax level (A) and total WBC count (B). Variables are those at the time of PET/CT staging. PET/CT = positron emission tomography/computed tomography, SUVmax = maximum standardized uptake value, WBC = white blood cell.
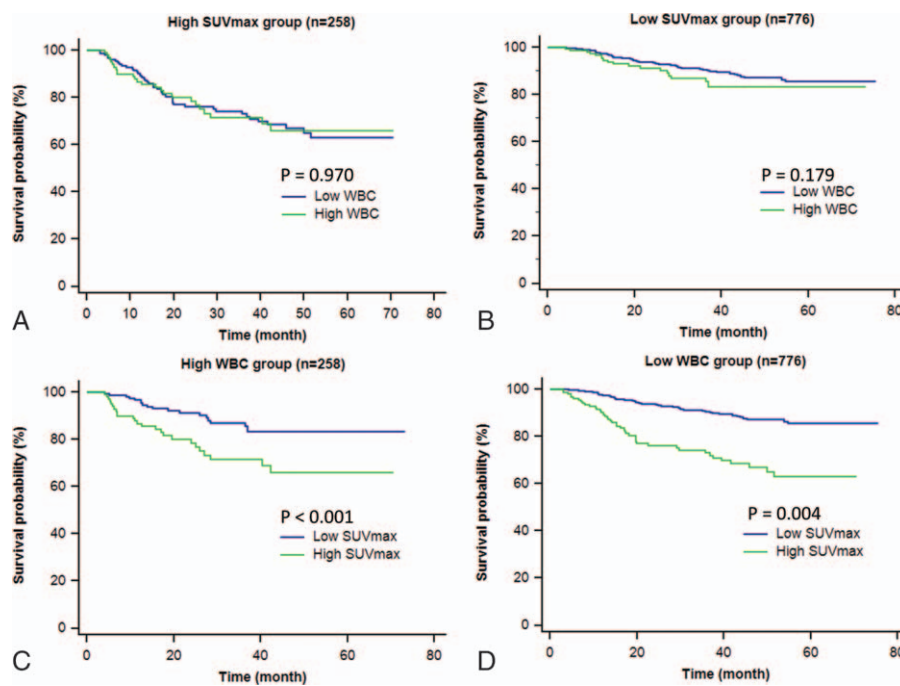
Figure 3. Kaplan–Meier curves of disease-free survival of study subjects categorized according to SUVmax and WBC levels. A, B, Survival curves of high SUVmax (n = 258; A) and low SUVmax groups (n = 776; B) stratified by WBC count. C, D, Survival curves of high WBC (n = 258; C) and low WBC groups (n = 776; D) stratified by SUVmax. SUVmax = maximum standardized uptake value, WBC = white blood cell.

prognostic information. In the study by Zhang et al,[20] PLR did not have independent prognostic value, even though NLR did. Conversely, the study by Cannon et al[21] found an association between nonlocal failure and PLR but not NLR. More recently, Sim et al[22] evaluated 250 NSCLC patients with EGFR mutations and found that NLR was a significant prognostic factor for first-line progression-free survival in the chemotherapy group, but not in patients treated with tyrosine kinase inhibitors.

The reason our study with a large number of patients only managed to show total WBC count as a prognostic indicator may be explained by difference in subject characteristics. Even previous reports with early-stage NSCLC patients may have some differences in study population compared with our study. For instance, although subjects in the study by Cannon et al[21] had early-stage NSCLC, they were medically inoperable patients who underwent stereotactic radiotherapy instead of curative surgery. Also, the rate of recurrence or deaths in our study cohort (13.9%) was lower than that of the study by Zhang et al[20] (50.1%) or the study by Cannon et al[21] (24.1%), which cannot be explained by differences in follow-up duration (29.5 months vs 46 months and 17 months). Furthermore, only a small portion of our patients (3.8%) had WBC counts exceeding >10,000/μL. These facts suggest that our study population had more favorable prognostic characteristics compared with those of previous studies.

Unlike the weak prognostic association of hematologic parameters, tumor SUVmax was confirmed to be a powerful prognostic factor with the highest hazards ratio. A close relation between high tumor SUVmax and poor outcome in patients with NSCLC is well recognized, and this has also been observed with early-stage disease.[23–26] In our study, a tumor SUVmax of 7.83 effectively stratified patients with favorable from those with poor

prognosis. This finding is similar to the report of Vansteenkiste et al,[25] who found a tumor SUVmax of over 7.0 to be associated with adverse outcome in NSCLC patients. High tumor SUVmax was a significant independent risk factor by multivariate analysis, along with old age and tumor stage 1B. Tumor SUVmax was also able to stratify favorable from poor outcome in both high and low WBC count groups. These results demonstrate that tumor FDG uptake remains a strong prognostic indicator in patients with resected stage I NSCLC after adjustment for hematologic parameters in addition to other clinical variables.

Limitations of our study include its retrospective design. Another potential limitation is the interval between PET/CT and blood tests, which reached 30 days in a few patients. However, the majority of our subjects had a much shorter interval, which averaged only 3.4 days. Only 3% of the subjects had an interval greater than 2 weeks, and during this interval, all were confirmed to be free of events that might affect blood counts such as infectious symptom, fever, trauma, blood loss, or medication. Also, the possibility that tumor SUVmax may have been underestimated by partial volume effect in some of the small tumors cannot be excluded. Finally, since our subjects were limited to stage I NSCLC, the prognostic impacts of tumor SUVmax and hematologic markers may be different in patients with more advanced disease. Therefore, further studies with patients with a broader range of NSCLC stage are required.

In patients with stage I NSCLC, circulating blood counts showed weak but significant correlation to tumor FDG uptake. Although total WBC count was a significant univariate risk factor, the prognostic value of tumor FDG uptake was substantially superior. Tumor SUVmax was an independent predictor of outcome after adjustment for other variables including WBC count, and effectively stratified prognosis in patients with low as well as high WBC count.

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